Supplementary Online Content

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eMethods. Supplementary Methods

This supplementary material has been provided by the authors to give readers additional information about their work.

Selection of eligible patients

Subjects for this study were eligible if they had one of seven life-limiting conditions (cancer, heart failure, COPD, AIDS/HIV, selected neurodegenerative, renal failure, liver failure) and excluded if their primary diagnosis indicated trauma or if they received a transplant during their admission.

Conditions, traumas and transplant procedures were identified through ICD-9 codes from the hospital databases. Specific ranges of ICD-9 codes for these factors are provided in eTable 1.

eTable 1. ICD-9 codes for identifying conditions, trauma and transplant in defining the sample

Conditions						
Cancer	140.x-172.x, 174.x-209.3x, 209.7x, 230.x-239.x, v58.0x (radiation), and v58.1x (chemo)					
	[Thus generally 140-239 plus radiation &					
	chemotherapy, but excluding benigns 209.4x-					
	209.6x, 210.x – 229.x, and 'other skin' 173.x]					
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03,					
	404.11, 404.13, 404.91, 404.93, 428.x					
COPD	416.8, 416.9, 490.x – 505.x, 506.4, 508.1, 508.8					
AIDS/HIV	042.x, 043.x, 044.x					
Neurodegenerative	290.x, 294.1x, 294.2x, 330x – 337x					
Renal	070.22, 070.23, 070.32, 070.33, 070.44, 070.54,					
	070.6, 070.9, 456.0-456.2, 570.x, 571.x, 572.2-					
	572.8, 573.3, 573.4, 573.8,573.9, V42.7					
Liver	403.01, 403.11, 403.91, 404.02, 404.12, 404.92,					
	585.x, 586.x, 588.0, V42.0, V45.1x, V56.x					
Trauma						
As primary dx	348.1, 800.x-904.x, 925.x-929.x, 940.x-959.x,					
	994.0, 994.1					
Transplant						
Bone marrow / stem cell:	41.00 – 41.09					
Heart:	37.50 – 37.59					
Lung:	33.50 – 33.59					
Heart-lung:	33.60 – 33.69					
Kidney:	55.60 – 55.69, 52.80					
Liver:	50.50 – 50.59					

Literature review and identification of studies to participate in meta-analysis

Prior reviews found that meta-analysis of palliative care consultation (PCC) effect on costs is not possible due to heterogeneity of approaches, populations and reporting¹² as well as concerns about methodological weaknesses.³⁴ Therefore studies were identified for participate in our meta-analysis through three sequential objectives:

- Literature search: To identify all economic evaluations of the PCC intervention for adult hospital inpatients to August 31st, 2017;
- ii. *Study selection:* To appraise all evaluations, and identify those that are suitable for methods incorporating intervention timing,³⁵ controlling appropriately for confounding⁴ and stratification by clinical factors;⁶⁷
- iii. Data access: To approach the lead author of each suitable study and invite collaboration via data-sharing and new analyses;

Literature search

We searched CENTRAL, PubMed, EconLit, EMBASE, CINAHL and PsycINFO and databases using terms from relevant domains (e.g., palliative, hospice; economic*, cost*) to search titles, abstracts and subject fields. For details of our replicable search strategy in each specific database, see eTables 2-7.

eTable 2. CENTRAL search strategy

Step	Subject heading or search term	# of studies returned
1	palliative care or end of life care or terminal care	3891
2	cost* or economic* or financial	89804
3	1 AND 2	1009
4	hospital or consult*	244785
5	3 AND 4	647
6	5 AND Limiters: Trials and Economic evaluations	372

Search conducted: December 21st, 2017

eTable 3. PubMed search strategy

Step	Subject heading or search term	# of studies returned
1	"palliative care"[Title/Abstract] OR "end of life care"[Title/Abstract] OR hospice[Title/Abstract] OR "terminal care"[Title/Abstract]	34784
2	cost*[Title/Abstract] OR economic*[Title/Abstract] OR financial[Title/Abstract]	702861
3	"palliative care"[MeSH Terms] OR "hospice care"[MeSH Terms] OR "terminal care"[MeSH Terms]	84370
4	"cost benefit analysis" [MeSH Terms] OR "cost savings" [MeSH Terms] OR "cost control" [MeSH Terms] OR "economics" [MeSH Terms] OR "health care costs" [MeSH Terms] OR "health resources" [MeSH Terms] OR "health services/economics" [MeSH Terms] OR "hospital costs" [MeSH Terms] OR "costs and cost analysis" [MeSH Terms]	578450
5	1 AND 2	3083
6	1 AND 4	2736
7	3 AND 2	3260
8	3 AND 4	5173
9	"palliative care/economics"[MeSH Terms] OR "palliative care/utilization"[MeSH Terms] OR "terminal care/economics"[MeSH Terms] OR "critical illness/economics"[MeSH Terms]	2477
10	5 OR 6 OR 7 OR 8 OR 9	9236
11	hospital*[Title/Abstract] OR consult*[Title/Abstract]	1147928
12	"2013/08/01"[Date - Publication] : "2017/08/31"[Date - Publication] AND "english"[Language] AND "journal article"[Publication Type]	4049216
13	10 AND 11 AND 12	665

eTable 4. EconLit search strategy

9	Step	Subject heading or search term	# of studies returned
	1	AB palliative care OR AB terminal care OR AB end of life care OR AB hospice care	80
	2	1 AND [Limiters - Published Date: 20130801-20170831; Publication Type: Journal Article]	17

eTable 5. EMBASE search strategy

Step	Subject heading or search term	# of studies returned
1	'palliative therapy':ab,ti OR 'terminal care':ab,ti OR 'hospice':ab,ti	18486
2	'cost':ab,ti OR 'economic':ab,ti OR 'financial':ab,ti	675823
3	'palliative therapy'/exp OR 'terminal care'/exp OR 'hospice'/exp	138920
4	'cost benefit analysis'/exp OR 'cost control'/exp OR 'economics'/exp OR 'health care cost'/exp OR 'health care planning'/exp OR 'hospital cost'/exp OR 'cost'/exp	643856
5	1 AND 2	1506
6	1 AND 4	1611
7	3 AND 2	5817
8	3 AND 4	7436
9	5 OR 6 OR 7 OR 8	11260
10	'hospital*':ab,ti OR 'consultation':ab,ti	1641036
11	9 AND 10	2975
12	11 AND 'article'/it	1444

Search conducted: December 21st, 2017

eTable 6. CINAHL search strategy

Step	Subject heading or search term	# of studies returned
1	MH cost savings OR MH cost benefit analysis OR MH (costs and cost analysis) OR MH Economics OR MH cost control OR MH health care costs OR MH health resource utilization OR MH health facility costs	95,918
2	MH hospice OR MH palliative care OR MH terminal care OR MH critical illness	46,991
3	1 AND 2	1,223
4	AB cost* OR AB econom* OR AB finan*	150,885
5	AB palliative OR AB terminal OR AB end of life OR AB hospice	35,485
6	4 AND 5	2,577
7	3 OR 6	3,506
8	7 AND [Limiters: Published between 2013/08/01 and 2017/08/31; English Language; Age Groups: All Adult; Publication type: Journal article]	262

eTable 7. PsycINFO search strategy

Step	Subject heading or search term	# of studies returned
1	TI (palliative care or end of life care or terminal care or hospice) OR AB (palliative care or end of life care or terminal care or hospice)	13499
2	TI (cost or economic or financial) OR AB (cost or economic or financial)	196871
3	MA (palliative care or end of life care or terminal care or hospice)	8880
4	MA cost benefit analysis OR MA cost savings OR MA cost control OR MA economics OR MA health care costs OR MA health resources OR MA health services research OR MA hospital costs OR MA (costs and cost analysis)	16593
5	1 AND 2	1080
6	1 AND 4	311
7	3 AND 2	647
8	3 AND 4	325
9	5 OR 6 OR 7 OR 8	1396
10	TI (hospital or consultation) OR AB (hospital or consultation)	131716
11	9 AND 10	351
12	Limiters: English; Journal article	320

Search conducted: December 21st, 2017

As shown in Figure 1 in the main manuscript, the six databases returned (372+665+17+1444+262+320=)3080 titles, the prior literature review included 10 titles added by hand and the approach to authors identified no additional studies of interest. The 3090 titles included 701 duplicates, leaving 2389 unique titles to review.

Two independent reviewers applied the same eligibility criteria as the prior review: (i) a credible economic evaluation of (ii) a specialist-led interdisciplinary palliative care consultation team for adult patients in (iii) the hospital inpatient setting, (iv) measuring the impact on costs, charges or other cost effectiveness measure and (v) assessing against a usual care (UC) comparator. Only Englishlanguage journal articles were considered.

Of 2389 unique titles, 2352 articles were rejected at title/abstract and 37 were reviewed at full text, of which 20 were excluded and 17 were classed as economic evaluations of PCC by our criteria.

These 20 excluded articles and their reasons for exclusion are provided in eTable 8:

eTable 8. Studies (n=20) identified via database search and rejected at full text screen

Study	Reason for exclusion
Bharadwaj, 2016 ⁸	(i) a series of case studies reporting limited details on data and methods.
Brick, 2017 ⁹	(v) no usual care comparator.
Bruera, 2000 ¹⁰	(ii) not a PCC intervention.
Colligan, 2017 ¹¹	(i) a series of case studies reporting limited details on data and methods.
Farquhar, 2014 ¹²	(iii) not hospital inpatients.
Farquhar, 2016 ¹³	(iii) not hospital inpatients.
Kondo 2015 ¹⁴	(ii) not a PCC intervention.
May, 2016 ⁶	Same study as ⁵ , which is included
May, 2016 ⁴	Same study as ⁵ , which is included
May, 2017 ¹⁵	Same study as ⁵ , which is included
May, 2017 ¹⁶	Same study as ⁵ , which is included
McGrath, 2010 ¹⁷	(ii) not a PCC intervention.
Mulvey, 2016 ¹⁸	(ii) not a PCC intervention.
O'Mahony, 2005 ¹⁹	(i) wide range of outcomes reported; limited scope to economics aspect.
Ozcelik, 2014 ²⁰	(i) an evaluation of patient outcomes reporting brief summary cost data only.
Ravakhah ²¹	(i) letter to the editor.
Rocque, 2015 ²²	(v) no usual care comparator.
Rosenberg, 2013 ²³	(i) wide-ranging summary with limited details on cost analysis.
Wang, 2016 ²⁴	(ii) not a consultation intervention.
Zalenski, 2017 ²⁵	(iii) ICU only.

Study selection

The 17 economic evaluations were appraised separately by two authors (PM and CN) for their suitability for re-analysis to a single methodological standard. The following additional criteria were therefore applied: (vi) patients' data were recorded and matched for a minimum set of confounders: age, gender, insurance status, primary diagnosis, and comorbidities; (vii) the data recorded both whether each participant received or did not receive palliative care, and if so what day of the admission the first consult occurred; (viii) study eligibility criteria defined according to baseline factors only and not according to discharge status; (ix) one outcome of interest was total direct hospital costs for an inpatient episode of care. Direct costs were chosen as the best indicator of

short-term resource use in a hospital setting - the outcome of interest that an intervention such as palliative care, in potentially changing treatment choices and discharge goals, can be hypothesized to effect. The alternatives to direct costs are total costs (direct plus indirect costs), which risk overestimating the magnitude of effects²⁶; daily costs, which give a distorted picture of resource use if treatment and comparison group differ in length of hospital stay ^{3 4}; and charges, which are widely seen as ill-suited to economic evaluation.^{27 28}

The results of this appraisal are presented in eTable 9: eight studies are suitable and nine are excluded.

eTable 9. Economic evaluations (n=17) appraised for suitability for meta-analysis

es.

Data access

The previous section identified eight economic evaluations that are suitable for inclusion in our meta-analysis.

The principal investigator (PI) for each of these eight studies was approached to participate in the meta-analysis. Of the eight, six accepted.^{5 7 35-37 42} One was unable to participate as their data are no longer available,³⁸ and one did not respond to multiple attempts at communication.⁴⁰

Definition of treatment variable with respect to timing

Background

Recent methodological work has demonstrated that the magnitude of estimated effect for PCC on cost of hospital admission is systematically associated with the time from admission to first consultation.³ The explanation for this phenomenon is clear and intuitive:

- Utilization data such as hospital costs are additive across the episode of care under study, so
 costs accrued from the point of admission are included in primary outcomes of interest total
 direct costs and daily direct costs (total direct costs/length of stay).
- Patients who receive a consultation later in the hospital stay therefore accrue more costs in
 proportional and absolute terms prior to receiving the intervention compared to patients
 who receive a consultation at admission (*ceteris paribus*). These costs are included in the
 outcome of interest but by definition cannot be affected by the treatment.³
- Additionally, hospital costs do not accrue evenly over a hospitalization, being highest at the point of admission.⁴⁴
 - Where patients can receive a first consult at any point in their admission, pooling all PCC patients into one treatment group and evaluating impact of PCC on hospital costs does not meaningfully specify the treatment and increases risk of a false negative (type I error) since the treatment group includes people who only received the intervention after accruing the overwhelming majority of their outcome of interest. ¹⁶

This determination raises concerns about early economic studies of PCC⁴ and is a key motivating factor in conducting this meta-analysis.

While the evidence on timing and cost-effect is clear, appropriate ways to manage the issue with observational data remains an ongoing subject of research. Two approaches are visible in the literature:

- I. Define the intervention as 'received first PCC on day *t* of admission'. In principle this approach offers the clearest definition of the intervention and therefore the most useful information. However, a problem is quickly apparent: once 0<*t*, it is not clear how to define the comparison group. If all usual care patients are included then this group will include patients whose length of stay (LOS)<*t*, and who therefore were never candidates for the intervention as defined. If instead usual care patients with *t*<=LOS are included then this is defining the sample by an outcome, raising endogeneity concerns.⁴
- II. Define the intervention as 'received first PCC within t days of admission'. This approach avoids the fundamental problem of (I), since all patients are admitted on day 0 and therefore all patients have the opportunity to receive a PCC within t irrespective of the value of t. Treatment and comparison groups can be defined according to clear rules. However, it has its own limitations. First, there are no clinical guidelines on which to base t. Setting t very narrowly, e.g. t<=1, arbitrarily excludes PC patients from the treatment group and reduces its sample size. But where t is increased so too increases heterogeneity of the interventions pooled and increases the risk of a type I error in evaluating the effect of timely PCC following admission. Second, it raises the question of how to handle late-consult PC patients – those who receive their first PCC team interaction after t days in hospital. They can be excluded from the analysis or re-categorized as controls. The former approach risks losing information and sample size, the latter approach may bias results to the null if PCC reduces costs from the point it is administered, which some studies have suggested. However, this can be managed through simple sensitivity analysis: confirming that key conclusions via one approach hold via the other.5

Defining our exposure group in this meta-analysis

Of the six studies included in our meta-analysis, three make some attempt at incorporating timing: McCarthy (2015) uses Method I above, and May (2015, 2017) use Method II.

In this meta-analysis, we employ Method II for the reasons outlined above: treatment and comparison groups can be defined according to clear rules and sensitivity analyses can confirm if approach to late-consult PC patients is impacting results.

The decision nonetheless remains: what value to place on t?

Optimally this decision would be made a priori but there are no clinical guidelines to do so.

As summarized above, in a single study analysis, defining *t* raises two competing concerns in estimating robust results: the larger *t* is set, the risk of a type I error is increased; the smaller *t* is set, the smaller are the treatment groups which arbitrarily excludes PC patients from the treatment group, undermines the power of the calculations and may weaken the balance of the propensity score. In a meta-analysis such as this, an additional concern arises that distributions of first consult timing may differ between studies: if in Study A all PC patients received the intervention on day 0 and in Study B all did so on day 10 then pooling results for impact of PCC within 10 days of admission in A and B may be pooling effects for substantively different treatments.

In the absence of clinical guidelines and in light of these concerns, we examined the distributions of first consult timing in our data but prior to estimating treatment effect estimates. We ran models with direct costs as an outcome of interest and a fixed list of independent predictors (Table 1 in the main manuscript) differentiated by how the treatment variable was defined (within 2|3|4|5|6 days of admission) and evaluated model performance on the Aikake Information Criterion (AIC) ⁴⁵ and model fit. Model performance did not substantively differ by timing. We therefore chose instead to set the value of t to manage sample size from those studies that were included in the data. We sought a minimum sample of 150 in each stratum, with a minimum of 10 in both treatment and © 2018 American Medical Association. All rights reserved.

comparison groups, also based on prior work^6). We found that t=3 is the smallest value (i.e. minimizing risk of a type I error) while still preserving sufficient sample size to perform all of our intended primary analyses in all (sub-)samples. If t were set with a value lower than 3 then some comorbidity sub-sample analyses would not be possible in some datasets (see also 'Multimorbidity analyses' in this Appendix). Patients were therefore included in the treatment group if they received a consultation within three days of admission and otherwise included in the comparison group. This decision was made prior to estimating any treatment effect.

Conclusion

There is no foolproof approach to incorporating PCC timing into analyses of observational data but doing so is essential to the integrity of results. The absence of timing-sensitive methods in most economic studies of PCC was a critical motivating factor in undertaking the meta-analysis. Our methods in this paper reflect the best approach so far developed: define the intervention as 'receiving PCC within *t* days of admission' prior to estimating treatment effects and perform sensitivity analyses to confirm robustness of key findings.

Multimorbidity analyses: stratification and evaluation

Background

In this meta-analysis we aimed to estimate the effect of PCC on direct hospital costs for sub-samples defined by comorbidity, following early studies that reported no impact of PCC for the sickest patients⁴ and a more recent study that found a larger effect for those with greater illness burden.⁶

All included studies recorded presence/absence of disease using ICD-9 codes and these were used to identify both primary diagnosis and comorbidities. We used the Elixhauser index to measure comorbidity counts; this is a widely used measure and has been shown to out-perform the most prominent alternative, the Charlson index, with routinely collected data.⁴⁷

Stratification

At the outset we aimed to group subjects as follows: Elixhauser total = 0/1, 2, 3......x (where x is the highest number of comorbidities with sufficient sample size for all datasets to support estimation of PCC effect on direct costs. We aimed for a minimum sample of 150 in each stratum, also based on prior work⁶). We hypothesized grouping those with 0 and 1 comorbidities together since in our experience, while it is possible to have one of the seven life-limiting conditions that are required for eligibility in our study and an Elixhauser total of 0, this is unusual. We did not set a value α priori for x, since the number of strata would vary according to sample size and Elixhauser distribution within each participating dataset (eTable 10).

eTable 10. Elixhauser comorbidity counts, by study, primary diagnosis and treatment group

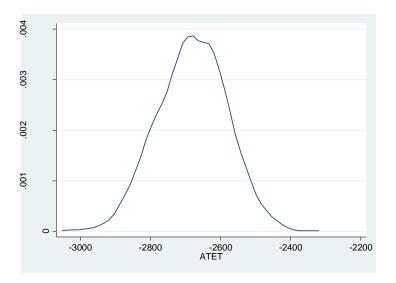
		5		37			5	5 7			42							
	NON	NC	CAI	NC	NOI	NC	CAI	NC	CAI	NC	NOI	NC	CAN	NC	NO	NC	CAI	NC
ET	UCn	PCn	Ucn	PCn	Ucn	PCn	Ucn	PCn	Ucn	PCn	Ucn	PCn	Ucn	PCn	Ucn	PCn	Ucn	PCn
0	2,516	56	7,581	251	473	4	429	11	52	1	29	0	375	2	34	3	53	0
1	7,557	217	9,945	378	1,217	9	620	33	120	13	1,135	9	2,156	16	226	13	237	12
2	10,941	295	7,846	423	1,711	24	564	38	122	35	3,122	34	3,228	72	644	25	519	22
3	10,108	278	4,681	287	1,709	45	381	33	148	43	4,025	67	2,550	122	885	33	496	42
4	7,147	211	2,180	149	1,034	29	235	18	135	53	3,243	102	1,743	136	820	32	388	33
5	4,185	127	1,036	71	509	14	91	8	95	46	2,001	84	907	85	582	26	198	22
6	2,013	63	423	22	207	3	35	1	59	14	1,023	50	382	57	324	13	55	8
7	768	27	133	10	64	1	15	0	35	13	416	27	173	20	148	8	21	3
8	236	5	34	4	22	1	5	0	15	4	110	17	52	4	37	1	9	1
9	49	1	7	0	4	1	1	0	7	4	31	1	13	0	22	0	2	0
10	10	0							4	1	4	1	3	0	3	1	1	0
11			2	0					1	0	0	1		1	1	0		1

Different studies supported different stratifications by Elixhauser distribution for cancer and noncancer groups, with eight strata (Elixhauser total = 0, 1, 2....7+) for samples where 150<N possible in both cancer and noncancer in one study.³⁵ By setting *x* at four, i.e. our comorbidity strata are 0/1 Comorbidities; 2 Comorbidities; 3 Comorbidities; 4+ Comorbidities, we are able to include all studies in eTable 10 (one sub-sample – NONC/ET1 in ³⁷ has nine PC patients and all others meet our a priori sought sample sizes). In examining the comorbidity strata for ³⁶ we found poor balance (i.e. consistently over 10% standardized difference on baseline confounders⁴⁸) between treatment and comparison groups due to low treatment group sample size and excluded this study from our comorbidity analyses. An alternative approach would have been to revise our original research questions and examine only two strata, e.g. 0-2 and 3+ comorbidities, for all six studies, but the team considered this unhelpfully narrowed the scope of those original questions. We prefer to examine four comorbidity strata in five studies than two strata in six studies.

Evaluation

Each regression output represents an ATET distribution which has a reported mean, bootstrapped standard error and sample size (all regression results are provided in the next section, 'Regression outputs'). This distribution can be reviewed graphically, e.g. eFigure 1.

eFigure 1. Probability density function for ATET in ALL sample, Morrison (2008)



In comparing ATET estimates for two sub-samples, i.e. CANC and NONC for any given study in Table 2 of the main manuscript, we use standard independent two-sample t-tests with the regression output. In pooling ATET estimates for a given set of sub-samples, e.g. CANC for all six datasets in Table 2 of the main manuscript, we combine the six distributions using mean ATET, SE and PCn.

In comparing the ATETs for four comorbidity strata (within ALL, CANC or NONC sub-samples), we used one-way ANOVA tests. This is a more conservative approach than alternatives, e.g. six head-to-head t-tests and allows us to examine not only the general association between Elixhauser totals and estimated ATET (which may not be linear in any case), and instead examine specific comparisons in post-hoc tests, e.g. does PCC estimated effect differ between ET1 and ET2 (single disease and multimorbidity) or ET1 and ET4 (single disease and high complexity) or both.

All pooled results, t-tests of difference and ANOVA results can be derived using the 'Regression outputs' in this data supplement.

Summary

In the abstract, an optimal approach to examining treatment effect heterogeneity by comorbidity counts would have incorporated a priori setting of the comorbidity strata. However, there are no clinical guidelines on which comorbidity count cut-offs could be specified and we sought to maximize © 2018 American Medical Association. All rights reserved.

the use of our available data. We therefore examines comorbidity counts in our datasets prior to treatment effect estimation and set cut-offs as 0/1, 2, 3 and 4+ as the approaches that maximized number of strata within all participating studies through sample size management. We evaluated differences between ATET estimates across strata using ANOVA one-way tests, which is a conservative way of evaluating differences in means between groups given sample sizes and standard errors.

In the main manuscript we detail our approach to treatment effect estimation for a given (sub)sample and study: in the weighted sample, we regress direct cost of hospital care on our

Regression outputs from our reported analyses (Tables 2 and 3 in main manuscript)

fixed list of predictors. We perform bootstrapping (1000 reps) in estimating the average treatment

primary independent variable (did the subject receive a PCC within three days of admission?) and a

effect on the treated (ATET).

In this section of the appendix, we provide the regression output for all ATETs in our primary analyses. That is:

- For each study we present the ATET for all subjects irrespective of diagnosis, for samples stratified by primary diagnosis cancer/noncancer, and (excluding Penrod 2010) samples stratified by Elixhauser.
- Results for all diagnoses and stratified by cancer/noncancer correspond directly to those reported in Table 2 in the main manuscript.
- Results by Elixhauser comorbidity total were pooled and presented (one pooled ATET per comorbidity stratum) in Table 3 in the main manuscript.

Data (mean ATET, distribution, sample size) presented here are sufficient to derive all pooled estimates and perform all tests of difference we report in the main manuscript. Note that sample size in any such calculation is the PCn, since the estimates are for the <u>treated</u>.

Morrison (2008)

eTable 11. Regression output from Morrison (2008) data

Sample	N	UCn	PCn	ATET	SE	Z	Р	lowCl	uppCl
ALL	82273	79398	2875	-2666	99	-27	<0.01	-2860	-2472
NONC	46810	45530	1280	-1868	147	-13	<0.01	-2156	-1581
CANC	35463	33868	1595	-3624	123	-29	<0.01	-3865	-3382
ALL/ET1	28501	27599	902	-2181	148	-15	<0.01	-2472	-1890
ALL/ET2	19505	18787	718	-2436	207	-12	<0.01	-2842	-2029
ALL/ET3	15354	14789	565	-2933	185	-16	<0.01	-3296	-2570
ALL/ET4	18913	18223	690	-3767	215	-18	<0.01	-4188	-3345
NONC/ET1	10346	10073	273	-1114	260	-4	<0.01	-1623	-605
NONC/ET2	11236	10941	295	-1054	361	-3	<0.01	-1762	-347
NONC/ET3	10386	10108	278	-2175	257	-8	<0.01	-2678	-1672
NONC/ET4	14842	14408	434	-3288	254	-13	<0.01	-3785	-2790
CANC/ET1	18155	17526	629	-2828	177	-16	<0.01	-3174	-2481
CANC/ET2	8269	7846	423	-3906	248	-16	<0.01	-4393	-3419
CANC/ET3	4968	4681	287	-4176	278	-15	<0.01	-4720	-3631
CANC/ET4	4071	3815	256	-5263	362	-15	<0.01	-5973	-4553

Penrod (2010)

eTable 12. Regression output from Penrod (2010) data

Sample	N	UCn	PCn	ATET	SE	Z	Р	lowCl	uppCl
ALL	6595	6449	146	-3716	1935	-2	0.06	-7509	77
NONC	5553	5499	54	-270	2919	0	0.93	-5992	5451
CANC	1042	950	92	-8651	2806	-3	<0.01	-14150	-3152

Morrison (2011)

eTable 13. Regression output from Morrison (2011) data

Sample	N	UCn	PCn	ATET	SE	Z	Р	lowCl	uppCl
ALL	9599	9326	273	-2853	1781	-2	0.11	-6344	638
NONC	7081	6950	131	-548	3078	0	0.86	-6580	5485
CANC	2518	2376	142	-5913	1929	-3	< 0.01	-9695	-2132
ALL/ET1	2796	2739	57	234	2146	0	0.91	-3973	4441
ALL/ET2	2337	2275	62	-3222	4091	-1	0.43	-11240	4795
ALL/ET3	2168	2090	78	-6189	3066	-2	0.04	-12197	-181
ALL/ET4	2298	2222	76	-6351	3724	-2	0.09	-13651	948
NONC/ET1	1703	1690	13	1118	3574	0	0.76	-5888	8123
NONC/ET2	1735	1711	24	-9797	8240	-1	0.23	-25948	6354
NONC/ET3	1754	1709	45	-1527	4045	0	0.71	-9456	6401
NONC/ET4	1889	1840	49	-399	5737	0	0.95	-11644	10846
CANC/ET1	1093	1049	44	-1517	2650	-1	0.57	-6712	3677
CANC/ET2	602	564	38	-2574	4353	-1	0.55	-11105	5957
CANC/ET3	414	381	33	-11850	4592	-3	0.01	-20850	-2850
CANC/ET4	409	382	27	-17394	4871	-4	<0.01	-26941	-7846

May (2015)

eTable 14. Regression output from May (2015) data

Sample	N	UCn	PCn	ATET	SE	Z	Р	lowCl	uppCl
ALL	1020	793	227	-3246	786	-4	<0.01	-4786	-1706
CANC/ET1	186	172	14	-340	3357	0	0.92	-6920	6239
CANC/ET2	157	122	35	-2783	1535	-2	0.07	-5792	226
CANC/ET3	191	148	43	-2241	1196	-2	0.06	-4585	103
CANC/ET4	486	351	135	-4535	1083	-4	<0.01	-6658	-2413

McCarthy (2015)

eTable 15. Regression output from McCarthy (2015) data

Sample	N	UCn	PCn	ATET	SE	Z	Р	lowCl	uppCl
ALL	27628	26721	907	-3112	470	-7	<0.01	-4033	-2190
NONC	15532	15139	393	-358	715	-1	0.62	-1760	1044
CANC	12096	11582	514	-4887	606	-8	<0.01	-6075	-3700
ALL/ET1	3722	3695	27	-2200	1811	-1	0.22	-5749	1349
ALL/ET2	6456	6350	106	-1294	1056	-1	0.22	-3365	776
ALL/ET3	6764	6575	189	-4479	571	-8	<0.01	-5598	-3359
ALL/ET4	10686	10101	585	-3469	675	-5	<0.01	-4793	-2145
NONC/ET1	1173	1164	9	-2342	1223	-2	0.06	-4739	55
NONC/ET2	3156	3122	34	1370	1711	1	0.42	-1984	4725
NONC/ET3	4092	4025	67	-2308	762	-3	<0.01	-3802	-814
NONC/ET4	7111	6828	283	-480	844	-1	0.57	-2135	1175
CANC/ET1	2549	2531	18	-1576	2914	-1	0.59	-7287	4135
CANC/ET2	3300	3228	72	-3289	968	-3	<0.01	-5186	-1393
CANC/ET3	2672	2550	122	-5188	803	-6	<0.01	-6761	-3614
CANC/ET4	3575	3273	302	-5901	998	-6	<0.01	-7857	-3946

May (2017)

eTable 16. Regression output from May (2017) data

Sample	N	UCn	PCn	ATET	SE	Z	Р	lowCl	uppCl
ALL	6003	5705	298	-9237	882	-10	<0.01	-10966	-7509
NONC	2122	1979	143	-10441	1566	-7	< 0.01	-13510	-7372
CANC	3881	3726	155	-6068	887	-7	< 0.01	-7807	-4329
ALL/ET1	578	550	28	-2871	1949	-1	0.14	-6691	949
ALL/ET2	1210	1163	47	-5536	1498	-4	<0.01	-8471	-2600
ALL/ET3	1456	1381	75	-6333	1828	-3	<0.01	-9917	-2750
ALL/ET4	2759	2611	148	-15040	1498	-10	<0.01	-17977	-12103
NONC/ET1	276	260	16	-2547	2789	-1	0.36	-8013	2918
NONC/ET2	669	644	25	-5681	2637	-2	0.03	-10849	-512
NONC/ET3	918	885	33	-5034	3579	-1	0.16	-12049	1980
NONC/ET4	2018	1937	81	-20599	2655	-8	<0.01	-25803	-15395
CANC/ET1	302	290	12	-3161	3762	-1	0.40	-10535	4212
CANC/ET2	541	519	22	-4508	1286	-4	<0.01	-7029	-1988
CANC/ET3	538	496	42	-7684	1864	-4	<0.01	-11338	-4030
CANC/ET4	741	674	67	-5340	1400	-4	<0.01	-8084	-2595

Sensitivity analyses for our reported analyses

We conducted four sensitivity analyses to check that our results were robust to factors that we did/could not control for in main analyses but considered potentially important:

- I. Use of propensity scores can distort results and increase risk of bias in certain conditions. 49 We therefore re-ran our analyses without propensity score weights (or an instrumental variable in the case of Penrod 2010). Results are given in eTable 17 and eTable 18.
- II. Magnitude of palliative care's cost-saving effect may be exaggerated by a proximity-to-death effect, if more PC patients than UC patients are considered to be at end of life and this impacts treatment decisions and discharge planning.^{35 37} We therefore re-ran our analyses without subjects who died during the index hospital admission. Results are given in eTable 19 and eTable 20.
- III. Two of eight studies that we identified did not participate in the meta-analysis: ³⁸ and ⁴⁰. To check that our results are robust to these studies being included and finding no difference, we re-ran our main analyses with our original six studies and two new studies: 'Study 7', which approximates to the sample size of ³⁸ and has an estimated ATET of 0; and 'Study 8', which approximates to the sample size of ⁴⁰ and has an estimated ATET of 0. Results are given in eTable 21.
- IV. Modelling approach. While nonlinear models are typically superior in managing the distributional properties of healthcare utilization in treatment effect estimation, choice of model may dictate treatment effect estimates particularly in management of skew and heteroscedasticity. We therefore re-ran our main ATETs analyses using standard OLS regression on square-root-transformed direct hospital costs and pooled the results. Results are give in eTable 22 and eTable 23.

In all cases the results do not differ substantively with our main analyses:

- In each pooled analysis for all subjects irrespective of primary diagnosis, PCC within three days of admission is estimated to reduce direct cost of hospital care for adults with seven life-limiting illnesses (p<0.01).
- This effect estimate is larger for those with a primary diagnosis of cancer than noncancer, and this difference is statistically significant (p<0.01).
- This effect estimate is larger for those with more comorbidities. When the sample is stratified into people with Elixhauser total [<=1 | 2 | 3 | 4<=], ANOVA tests find the differences between groups to be significant, and post-hoc tests find that head-to-head differences are significant between those with 4 or more comorbidities than those with two, or fewer than two.

eTable 17. Sensitivity analysis to balancing strategies: Table 2 from the main manuscript, ATETs estimated without propensity scores/instrumental variable and pooled

CI	t-test
-1839	<0.01
5603	0.24
11593	0.02
1393	<0.01
-6375	0.07
-1346	<0.01
	-1839 5603 11593 1393

t-test evaluates difference between CANC AND NONC; pooled estimates are the mean and 95%Cis of the combined ATET distributions.

eTable 18. Sensitivity analysis to balancing strategies: Table 3 from the main manuscript, pooling ATETs estimated without propensity scores

				Pooled ATI	ET	One-way ANOVA	Tuke	y HSD Post-hoc	Test
ALL	UCn	PCn	ATET (\$)	95%	CI		Elix<=1 vs.	Elixh=2 vs.	Elix=3 vs.
ET1	34755	1028	-2806	-3455	-2156				
ET2	28697	968	-2119	-2931	-1307	F(3,4576)= 4.6,	0.73		
ET3	24983	950	-3125	-3995	-2256	p<0.01	0.96	0.42	
ET4	33508	1634	-4190	-5042	-3339		0.08	<0.01	0.27

Comorbidity analyses with five studies, excluding ³⁶ as in main analysis as balancing not supported.

eTable 19. Sensitivity analysis to proximity to death: Table 2 from the main manuscript, ATETs estimated without subjects who died during index admission (no propensity scores)

ALL	UCn	PCn	ATET	95%	CI						
35	73,917	1863	-2653	-2950	-2357						
36	2,816	48	-7156	-15566	1255						
37	8,790	215	1179	-2429	4788						
5	758	211	-1660	-3009	-311						
7	25,729	788	-2524	-3685	-1362						
42	5,617	292	-9859	-11975	-7743						
Pooled	117,627	3,417	-3000	-3457	-2543						
	CANC					NONC					
	UCn	PCn	ATET	95%	CI	UCn	PCn	ATET	95%	CI	t-test
35	32,059	1106	-4413	-4754	-4072	41858	757	-1473	-1923	-1022	0.00
36	2,647	19	-20433	-34419	-6447	108	90	-3949	-15088	7190	0.08
37	2,217	125	-2982	-6735	772	6663	0	4148	-2182	10478	0.06
5	758	211	-1660	-3009	-311						
7	1,669	444	-4349	-5629	-3070	3452	344	-737	-2806	1331	0.00
42	11,360	143	-6011	-8357	-3664	14985	29	-9777	-13378	-6176	0.09
Pooled	50,710	2048	-4376	-4847	-3906	66,917	1369	-1875	-2733	-1016	0.00

t-test evaluates difference between CANC AND NONC; pooled estimates are the mean and 95%Cis of the combined ATET distributions.

eTable 20. Sensitivity analysis to proximity to death: Table 3 from the main manuscript, ATETs estimated without subjects who died during index admission (no propensity scores)

				Pooled ATI	E T	One-way ANOVA	Tuke	y HSD Post-hoc	Test
ALL	UCn	PCn	ATET (\$)	95%	CI		Elix<=1 vs.	Elixh=2 vs.	Elix=3 vs.
ET1	33297	728	-2518	-3103	-1933				
ET2	27218	691	-2081	-2925	-1238	F(3,3365)= 4.2,	0.92		
ET3	23567	717	-2988	-3860	-2117	p<0.01	0.90	0.55	
ET4	30729	1233	-4063	-4971	-3156		0.05	<0.01	0.29

Comorbidity analyses with five studies, excluding ³⁶ as in main analysis as balancing not supported.

eTable 21. Sensitivity analysis to excluded studies: Table 2 from the main manuscript, pooled ATETs estimated with two additional studies finding no effect of intervention in either direction

ALL	UCn	PCn	ATET	95%	CI						
35	79,398	2,875	-3333	-3586	-3080						
36	6,449	146	-6246	-10483	-2009						
37	9,326	273	3083	-1509	7676						
5	793	227	-2110	-3479	-742						
7	26,721	907	-2359	-3549	-1168						
42	5,705	298	-9794	-11864	-7725						
'Study7'	1,803	1,802	0	0	0						
'Study8'	4,431	1,477	0	0	0						
Pooled	134,626	8,005	-1918	-2125	-1711						
	CANC					NONC					
	UCn	PCn	ATET	95%	CI	UCn	PCn	ATET	95%	CI	t-test
35	33,868	1,595	-5132	-5428	-4837	45,530	1,280	-2214	-2589	-1839	<0.01
36	950	92	-12145	-17839	-6450	5,499	54	-4929	-15460	5603	<0.01
37	2,376	142	-5121	-10918	675	6,950	131	4989	-1615	11593	<0.01
5	793	227	-2110	-3479	-742						
7	11,582	514	-4431	-5819	-3043	15,139	393	-630	-2653	1393	<0.01
42	1,979	143	-5941	-8292	-3589	3,726	155	-9823	-13271	-6375	<0.01
'Study7'	310	310	0	0	0	1,493	1,492	0	0	0	1.00
'Study8'	886	289	0	0	0	3,545	1,158	0	0	0	1.00
Pooled	52,744	3,312	-3482	-3827	-3137	81,882	4,663	-909	-1166	-652	<0.01

t-test evaluates difference between CANC AND NONC; pooled estimates are the mean and 95%Cis of the combined ATET distributions. Results for six included studies are the same as in main manuscript. 'Study 7' estimates sample sizes for ³⁸ from overall reported sample size of 3605, 17% primary cancer prevalence and 50% palliative care referrals. 'Study 8' estimates sample sizes for ⁴⁰ from reported sample sizes of UCn=4,431, PCn=1,477 and 20% primary cancer prevalence. PC timing not reported in either study; all PC patients assumed to have received PC within 3 days of admission for inclusion in treatment group in this table.

eTable 22. Sensitivity analysis to model selection: Table 2 from the main manuscript, ATETs estimated with OLS regression and square-root direct costs as outcome of interest

ALL	UCn	PCn	ATET	95%	CI						
35	79,398	2,875	-13.5	-14.5	-12.5						
37	9,326	273	-3.8	-12.7	5.0						
5	793	227	-13.4	-19.9	-6.9						
7	26,721	907	-8.7	-12.0	-5.4						
42	5,705	298	-29.0	-34.6	-23.3						
Pooled	121,943	4,580	-13.0	-14.2	-11.8						
	CANC					NONC					
	UCn	PCn	ATET	95%	CI	UCn	PCn	ATET	95%	CI	t-test
35	33,868	1,595	-18.2	-19.5	-16.9	45,530	1,280	-9.4	-11.0	-7.7	<0.01
37	2,376	142	-9.3	-19.9	1.3	6,950	131	-3.0	-17.4	11.4	0.49
5	793	227	-13.4	-19.9	-6.9						
7	11,582	514	-16.9	-21.2	-12.6	15,139	393	3.5	-1.4	8.5	<0.01
42	1,979	143	-18.4	-25.4	-11.4	3,726	155	-32.9	-41.5	-24.3	0.01
Pooled	50,598	2,621	-17.0	-18.4	-15.6	71,345	1,959	-8.2	-10.1	-6.3	<0.01

t-test evaluates difference between CANC AND NONC; pooled estimates are the mean and 95%Cis of the combined ATET distributions.

eTable 23. Sensitivity analysis to proximity to death: Table 3 from the main manuscript, ATETs estimated with OLS regression and square-root direct costs as outcome of interest

				Pooled ATE	Τ	One-way ANOVA	Tuke	y HSD Post-hoc	Test
ALL	UCn	PCn	ATET (\$)	95%	CI		Elix<=1 vs.	Elixh=2 vs.	Elix=3 vs.
ET1	34755	1028	-9.5	-11.3	-7.8				
ET2	28697	968	-10.3	-12.6	-8.0	F(3,4576)= 5.3,	p=0.97		
ET3	24983	950	-13.2	-15.4	-10.9	p<0.01	p=0.13	p=0.34	
ET4	33508	1634	-14.8	-17.0	-12.7		p<0.01	p=0.02	p=0.73

Comorbidity analyses with five studies, excluding ³⁶ as in main analysis as balancing not supported.

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